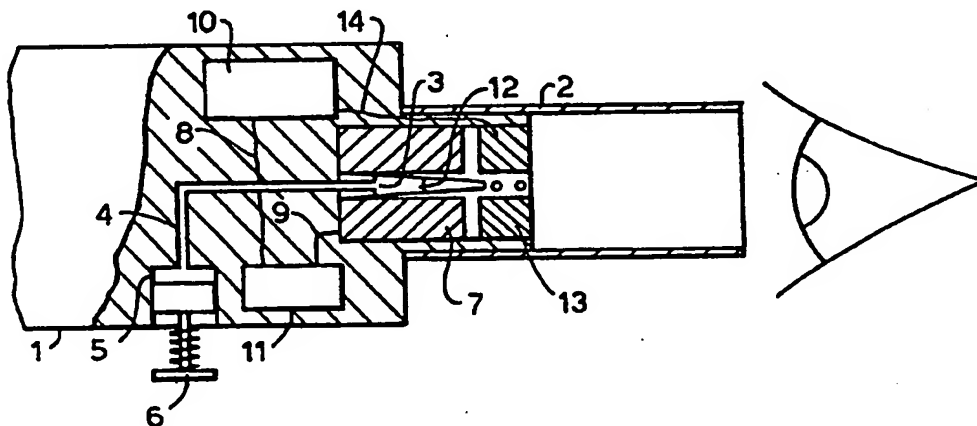


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(54) Title: **AQUEOUS OPHTHALMIC SPRAYS**

## (57) Abstract

A method of administering to the eye a liquid ophthalmic formulation, comprising an ophthalmologically acceptable liquid and optionally containing an ophthalmologically-active substance, characterized in that the formulation has a viscosity in the range  $10^{-3}$  to  $1.0$  Pa.s and a resistivity lower than  $10^4$  ohm.cm, and that a jet of the formulation is ejected towards the eye, from a spray nozzle (12) situated adjacent to a piezoelectric or electromagnetic transducer (7), to form a stream of uniformly-sized, equally spaced, uncharged droplets, the stream of uncharged droplets is subsequently directed past a charging electrode (13) to induce an electric charge on each droplet in the stream, and the charged droplets discharge their electric charge by earthing on contact with the eye; and spraying apparatus suitable for use in that method.

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## TITLE: AQUEOUS OPHTHALMIC SPRAYS

This invention relates to a method of spraying aqueous solutions or suspensions to the eye, and apparatus suitable for the delivery of such sprays.

A conventional method of ocular administration of aqueous solutions or suspensions comprises the use of eye drops. This is generally known to have low patient acceptability, especially in the young, and it is necessary, for administration, to incline the recipient's head towards a horizontal position. The administration of a large drop of liquid to the eye initiates a blink reflex, which can result in a substantial wastage of the applied liquid or suspension by drainage either through the tear ducts or onto the skin surface. Indeed, it has been reported that if a 30-50 $\mu$ l drop is applied to the eye, the actual volume that remains at the target is only 5-7 $\mu$ l. Therefore, in addition to the low patient acceptability, there is a 4- to 10-fold wastage. This leads to inefficiency in the use of expensive ingredients and, in addition, the administrator has little control, and is uncertain, over the amount of liquid which actually reaches the target. This is particularly important if the liquid is a solution or suspension of an ophthalmologically-active therapeutic substance.

Another conventional method of ocular administration of an ophthalmologically-active therapeutic substance comprises the use of an ointment. This similarly has been found to have low patient acceptability and, in this method also, a substantial wastage of active ingredient can result.

These problems in the efficient administration of therapeutically active substances to the eye are largely overcome in European Patent No. 0 224 352B by generating a spray of electrically charged droplets of a liquid formulation comprising an ophthalmologically-active substance and an ophthalmologically-acceptable diluent, for subsequent administration to the eye. The formulation has a viscosity in the range  $10^{-3}$  to 1.0Pa.s at 25°C, and a resistivity in the range  $10^4$  to  $10^{12}$  ohm.cm at 25°C. The formulation is applied to a spray nozzle wherein a sufficiently large electrical

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potential relative to earth is applied to the formulation from a high voltage generator, that sufficient electrical gradient is produced at the nozzle to atomize the formulation as a spray of electrically charged droplets.

Although such a method allows the delivery to the eye of an optimum small volume of a formulation of a therapeutic substance, without requiring the recipient's head to be inclined towards the horizontal, it does, however, still have some drawbacks. Solutions or suspensions containing more than about 50% of water, that is, of lower resistivity than  $10^4$  ohm.cm, cannot be sprayed, and high voltages of 15kV or higher are used. Further, an electrode needs to be in contact with the formulation, to achieve the correct voltage for atomization, and this could cause cross-contamination problems for pharmaceutical formulations. A further disadvantage is that a formulation containing substantial amounts of non-aqueous solvents, which is to be dispensed by this method, is likely to be hypertonic, which although acceptable for very low volume applications can result in a stinging sensation if larger volumes are administered to the eye.

The present invention provides accurate dispensing of a low volume of a solution or suspension to the eye without the above-mentioned drawbacks. In particular the present invention allows the dispensing of isotonic solutions, which avoids stinging sensations, it allows the use of suspensions as well as solutions, and it offers manufacturing and environmental advantages by the reduced use of non-aqueous solvents. This is achieved by a process which involves the production of a colinear stream of uniformly-sized, equally spaced droplets of a liquid formulation, using either piezoelectric or electromagnetic transducers to cause uniform break-up of a jet of the formulation emitted from a nozzle. The droplets so produced are initially not electrically charged, and charging is accomplished subsequently by passing the stream of droplets through a cylindrical charging electrode longitudinally positioned so that induced electric charges are trapped on the droplets as they pass through the cylindrical electrode.

As indicated above, conventional methods for ocular administration lead to wastage of ingredient, for example by drainage

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through the naso-lachrymal duct into the throat, and subsequent ingestion into the gastro-intestinal tract, whence it can be absorbed systemically and exert undesired side-effects. For example, it is well documented in the literature that  $\beta$ -adrenoceptor antagonists administered as eye-drops can exert a significant cardiovascular effect as a result of such ingestion into the gastro-intestinal tract.

The present invention enables accurate targetting of a fine spray of electrically charged droplets of a liquid formulation to dose just the required amount of an ophthalmologically active substance, thereby substantially eliminating unwanted side-effects.

Thus, according to the invention, there is provided a method of administering to the eye a liquid ophthalmic formulation, comprising an ophthalmologically acceptable liquid and optionally containing an ophthalmologically-active substance, characterized in that the formulation has a viscosity in the range  $10^{-3}$  to 1.0 Pa.s and a resistivity lower than  $10^4$  ohm.cm, and that a jet of the formulation is ejected towards the eye, from a spray nozzle situated adjacent to a piezoelectric or electromagnetic transducer, to form a stream of uniformly-sized, equally spaced, uncharged droplets, the stream of uncharged droplets is subsequently directed past a charging electrode to induce an electric charge on each droplet in the stream, and the charged droplets discharge their electric charge by earthing on contact with the eye.

The method may be carried out in a unit dose mode, by charging the nozzle with a unit dose from an external source each time it is used, or in multi-dose mode, in which case a reservoir of the formulation supplies a unit dose to the spray nozzle each time the method is carried out.

The liquid ophthalmic formulation may be a hygiene product, for example an eyewash or artificial tears for the treatment of dry eye, or a moistening or lubricating product for contact lens users, in the form of a conventional, predominantly aqueous and essentially isotonic liquid preparation, or it may be a product containing an ophthalmologically-active substance.

The ophthalmologically active substances encompassed by this invention are any compounds having a pharmacological effect on and/or

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in the eye. Typical of such compounds are chemotherapeutic agents, compounds to aid ocular examination, and compounds to aid surgery, for example:

- (a) anti-inflammatory agents, such as prednisolone and other corticosteroids;
- (b) antimicrobial drugs, such as antibiotics, antiseptics, antivirals, fungicides and sulphonamides, for example chloramphenicol, sulphacetamide, gentamycin, nystatin, acyclovir and idoxuridine;
- (c) autonomic drugs, such as  $\beta$ -adrenoceptor antagonists, cycloplegics, miotics, mydriatics and vasoconstrictors, for example timolol, atenolol, pilocarpine, atropine, tropicamide, hyoscine, ephedrine, phenylephrine, carbachol, guanethidine and adrenaline;
- (d) local anaesthetics, such as lignocaine or oxybuprocaine;
- (e) diagnostics, such as fluorescein;
- (f) drugs to assist healing of corneal abrasions, such as urogastrone and epidermal growth factor (EGF);

of which (c) is a particularly important group.

Suitably, the ophthalmologically active substance is present in the formulation in a concentration range of from about 0.1% to about 20%, and preferably from about 5% to about 10%, but the required concentration depends, naturally, upon the potency of the particular active substance being used.

A resistivity lower than  $10^4$  ohm.cm for the liquid ophthalmic formulation is achieved by making it predominantly aqueous, although a small proportion of non-aqueous liquids, up to about 20%, may also be incorporated. Suitable such non-aqueous liquids are, for example, glycerol, propylene glycol, polyethylene glycol of average molecular weight up to about 600, and dimethyl isosorbide.

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The viscosity of the formulation may be adjusted to within the required range by the addition of viscolysers, for example hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinyl alcohol, polyethylene glycol, dextran or polyvinylpyrrolidone.

The tonicity of the formulation may be adjusted into the range tolerated by the eye, for example tonicity equivalent to 0.2-1.4% w/v sodium chloride, by the addition of a tonicity modifier. A preferred range of tonicity is equivalent to from 0.6-1.0% w/v sodium chloride, and especially preferred are solutions having a tonicity as close as possible to 0.9% w/v sodium chloride. A suitable tonicity modifier is, for example, sodium chloride itself. The addition of sodium chloride as a tonicity modifier also has the effect of lowering the resistivity of the formulation.

The formulation may also contain a preservative, for example benzalkonium chloride, chlorhexidine acetate, phenylmercuric acetate, phenylmercuric nitrate, thiomersal, chlorbutol, benzyl alcohol or p-hydroxybenzoates.

The formulation may also contain a pH buffer salt, to maintain the pH of the formulation at an optimum to minimize chemical degradation, to increase comfort for the user, and to enhance therapeutic effect. Suitable such buffer salts are, for example, borate buffer (boric acid/borax), phosphate buffer (sodium hydrogen phosphate/sodium phosphate) and citrate buffer (citric acid/sodium citrate).

Several drugs used in ophthalmic formulations oxidize on exposure to air, with loss of potency, and the formulation may therefore advantageously contain an antioxidant, for example sodium metabisulfite for acid formulations, or sodium sulfite for alkaline formulations.

A chelating agent, for example disodium edetate, may also be included, to remove traces of heavy metals, where the presence of such impurities catalyses the breakdown of the drug. Disodium edetate also has the effect of enhancing the activity of certain preservatives, and the concentration of benzalkonium chloride, for example, may be reduced when disodium edetate is also present in the formulation.

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According to a further feature of the invention there is provided an apparatus for carrying out the method described above. The invention thus provides spraying apparatus for dispensing a liquid formulation to the eye, as described above, which comprises:

- (i) at least one spray nozzle having an outlet of sufficiently small cross section to be capable of retaining an appropriate amount of a liquid formulation, by surface tension;
- (ii) means to supply an appropriate measured volume of a liquid formulation to the spray nozzle;
- (iii) means to eject a measured volume of liquid formulation from the spray nozzle as a jet;
- (iv) means for exciting the jet of liquid formulation emitted from the spray nozzle to form a stream of droplets of liquid formulation;
- (v) a charging electrode spaced co-axially in front of the spray nozzle, and so spaced that the stream of droplets, immediately they are formed, are within the charging field of the electrode; and
- (vi) means for applying a voltage to the electrode.

In one embodiment of this invention, the means to supply an appropriate measured volume of a liquid formulation is provided by a metered valve or syringe-pump of the type used for multi-dose administration of insulin, to control the passage of the liquid formulation from a reservoir in the apparatus, to the spray nozzle. Alternatively, accurately measured low volumes can be supplied to the apparatus by placing the spray nozzle in the liquid formulation and drawing in the required volume by pipette action, for example by using a piston in a syringe.

In a preferred aspect of this invention, we have found that the best spraying results are achieved using a modification of the previous apparatus, in which the spray nozzle is demountable from the apparatus. In use the required volume of formulation is placed in the demounted spray nozzle, which is then located on the spraying apparatus in any convenient manner, such as by screwing or by friction-fit on an appropriate receiving member. In this way, the low



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volume of formulation is measured in any convenient manner prior to use.

Piston action can also be used as the means to eject a measured volume of liquid formulation from the spray nozzle as a jet.

The means for exciting the the jet of liquid formulation emitted from the spray nozzle to form a stream of droplets of liquid formulation may, for example, a piezoelectric or an electromagnetic transducer. For optimum droplet generation, the jet of liquid formulation needs to be perturbed at a wavelength equal to 9.016 times the radius of the spray nozzle, so that, for example, for a nozzle of approximately 100 $\mu$ m diameter, frequencies of 1-200kHz, preferably 50-150kHz, are required.

The charging electrode which is spaced co-axially in front of the spray nozzle conveniently takes the form of a cylinder or annulus, co-axial with the spray nozzle, charged to a suitable positive or negative potential, but it may also be in the form of separate elements of any suitable form, located around the axis of the nozzle, and with a space between, through which the stream of droplets can be directed in order to acquire an electrical charge. As indicated above, for efficient use of the formulation, that is, so that all of the active ingredient reaches the treatment site, it is necessary that each droplet in the stream becomes electrically charged as soon as it is formed from the jet, so the charging electrode must be located in front of the nozzle so that immediately a droplet is formed, it is within the charging field of the charging electrode.

The resistivity of the liquid formulation must be chosen to be low enough to ensure that the droplets become fully charged within the duration of the charging electrode pulse, which will typically be 2-4 $\mu$ s. It can be shown mathematically that, for a given geometry, the charge on the droplets is determined solely by the voltage applied to the charging electrode. For droplets of approximately 100 $\mu$ m diameter, charging voltages in the range of about 0.1 to about 1000V are suitable, modulated at the same frequency as the drop generation rate, that is, the transducer frequency, or some sub-harmonic of it. Resistivities for the liquid formulation of less than 10<sup>4</sup> ohm.cm, and preferably in the range of 10<sup>2</sup> to 10<sup>3</sup> ohm.cm, are required in order for

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the droplets to become fully charged.

Generally, in the apparatus of this invention, at least the spray nozzle is suitable to be hand-held when in use, and comprises one or two spray nozzles, depending upon whether it is desired to treat eyes separately or concurrently. Conveniently, the voltage required to charge the charging electrode is provided by a battery powered voltage generator, housed in hand-held apparatus. In another embodiment, the voltage can be generated in a remote pack, and supplied by an electrical connection to a hand-held spraying apparatus. In another embodiment, the reservoir supplying the formulation to the spray nozzle may be remote from the hand-held spray nozzle, and connected thereto by appropriate flexible tubing. In another embodiment, both the voltage generator and the reservoir may be remote from the hand-held spray nozzle.

A particular embodiment will now be described, by way of example only, with reference to Figure 1, which is a schematic view illustrating the principal components of one form of the apparatus.

Referring to Figure 1, there is a body member 1 of a suitable size to be hand-held. On one wall of the body member 1 there is mounted a guide 2 in the form of a short tube, the diameter of which approximates to the size of the eye to be treated. In the portion of the wall of the body member 1 which lies within the guide tube 2 there is positioned centrally the outlet 3 of a narrow bore tube 4 which at its other end broadens to provide a wider bore section 5, positioned in a side wall of the body member 1, and in which a spring-loaded piston 6 can operate. Located in the wall of the body member 1, and disposed around the outlet 3 of the narrow bore tube 4 in an annular manner is a piezoelectric or electromagnetic transducer 7, which is powered through electrical connections 8 and 9 from a voltage generator 10 via a frequency control unit 11, both of which are housed within the body member 1. A demountable nozzle 12 is provided which is capable of being detached from the apparatus in order to be charged with the formulation to be administered, and then re-attached securely within the central orifice of the transducer, by a tight push fit, to cooperate with the outlet 3 of the narrow bore tube 4. Within the guide tube 2, adjacent to the transducer 7 and

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separated therefrom by a small distance, is an annular or cylindrical charging electrode 13, located co-axially with the transducer 7, and electrically insulated from the other parts of the apparatus. The charging electrode 13 is charged to suitable positive or negative potential through an electrical connection 14 from the voltage generator 10, and its pulse frequency is controlled through the frequency control unit 11.

In use, the demountable nozzle 12 is filled with the appropriate volume of the formulation to be administered, the apparatus is held in the hand, and the guide tube is positioned directed towards the eye to be treated, and a short distance therefrom. The voltage generator 10 is switched on, to activate the transducer 7 and the charging electrode 13. The piston 6 is then depressed against its spring, to create sufficient pressure within the narrow bore tube 4 to expel the liquid formulation from the nozzle 12, through the central orifice of the transducer 7, whereby the jet of liquid formulation is broken up to produce a colinear stream of uniformly sized, equally spaced, uncharged droplets. The stream of droplets then passes through the bore of the annular charging electrode 13, where each droplet acquires an electric charge. The frequency control unit 11 is pre-adjusted to ensure that the voltage on the charge electrode is varied at the same frequency as, or a greater frequency than, that at which the droplets are produced, so that each droplet is individually electrically charged. The charged droplets then continue towards the eye to be treated, where they discharge their electric charge at the first earthed surface they encounter, namely the tissue of the eyeball, to give the eyeball an even coating of the formulation, without sensation.

The invention will now be illustrated, but not limited, by the following Example:

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Example 1

Ephedrine hydrochloride (0.25mg) was formulated as a 5% solution in physiological saline, radiolabelled with approximately 0.8Gbg of  $^{99m}\text{Tc}$ -DTPA complex. This formulation was sprayed, from apparatus essentially as hereinbefore specified, onto one eye of each of 6 New Zealand white rabbits, according to the following procedure:

The test animals were acclimatised to the experimental conditions, by exposure to constant light intensity and minimal distractions, for 20 minutes. They were then placed in restraining boxes which were positioned approximately 30-40cm in front of a camera (Pentax ME Super 35mm camera fitted with an SMC Pentax 50mm lens and 2x converter) set up on a tripod. A scale of known magnitude was placed next to, and in the same plane as, the pupil, prior to photographs being taken.

The animals were allowed to settle, and photographs were taken at f12 and 1/15 second, using ISO400 film (Kodak Gold 400). Photographs were taken 5 minutes prior to dosing of the ephedrine formulation, in order to allow determination of baseline (control) pupil diameters. The ephedrine formulation (5µl) was then administered to the eye as a pulse of charged droplets generated from the apparatus of the invention described above, and photographs taken at intervals over the next 3 hours.

Pupil diameters were determined from the developed colour prints (approximately 15x10cm) using an electronic micrometer (Digimatic Caliper, Mitutoyo Corp., Japan). Absolute pupil diameters were established by comparing the pupil diameter with the known scale on the photographs. From these measurements, the maximum response ratio was determined from the relationship:

$$RR_{\max} =$$

$$\frac{(\text{pupil diameter at time } t) - (\text{average pupil diameter at time } t_0)}{(\text{average pupil diameter at time } t_0)}$$

The following results were obtained:

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RRmax								
<u>Animal</u>								
No.	1	2	3	4	5	6	Mean	SD*
Time (min)								
0	0.00	0.00	0.00	0.00	-0.04	0.00	-0.01	0.01
18	0.09	0.03	0.11	0.40	0.17	0.11	0.15	0.13
38	0.24	-0.15	0.15	0.48	0.13	0.11	0.16	0.20
59	0.35	0.29	0.09	0.52	0.15	0.15	0.25	0.16
80	0.14	-0.05	0.03	0.18	-0.16	0.10	0.04	0.13
102	0.11	-0.07	0.01	0.15	0.02	0.02	0.04	0.08
120	0.13	-0.06	0.13	0.01	0.05	-0.03	0.04	0.08
140	0.11	-0.11	0.02	0.25	-0.02	-	0.05	0.13
160	0.10	-0.12	0.11	0.15	-0.14	-0.08	0.00	0.13
180	0.04	-0.14	-0.02	0.26	-0.11	-0.12	-0.02	0.14

\* = standard deviation.

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These results are presented graphically in Figure 2, and show a marked mydriatic response in the measurements taken at 18, 38 and 59 minutes in all animals, and a continuing effect up to 80 minutes in some animals, after the administration of only 5 $\mu$ l of the ephedrine formulation by the method of this invention, which is a much lower volume than that normally required with conventional modes of application.

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CLAIMS

1. A method of administering to the eye a liquid ophthalmic formulation, comprising an ophthalmologically acceptable liquid and optionally containing an ophthalmologically-active substance, characterized in that the formulation has a viscosity in the range  $10^{-3}$  to 1.0 Pa.s and a resistivity lower than  $10^4$  ohm.cm, and that a jet of the formulation is ejected towards the eye, from a spray nozzle situated adjacent to a piezoelectric or electromagnetic transducer, to form a stream of uniformly-sized, equally spaced, uncharged droplets, the stream of uncharged droplets is subsequently directed past a charging electrode to induce an electric charge on each droplet in the stream, and the charged droplets discharge their electric charge by earthing on contact with the eye.
2. A method as claimed in claim 1 wherein the liquid ophthalmic formulation is a hygiene product.
3. A method as claimed in claim 1 wherein the liquid ophthalmic formulation is a product containing an ophthalmologically-active substance.
4. A method as claimed in claim 3 wherein the ophthalmologically-active substance is selected from anti-inflammatory agents, antimicrobial drugs, autonomic drugs, local anaesthetics, diagnostics and drugs to assist the healing of corneal abrasions.
5. Spraying apparatus suitable for dispensing a liquid formulation to the eye by the method claimed in claim 1, which comprises:
  - (i) at least one spray nozzle having an outlet of sufficiently small cross section to be capable of retaining an appropriate amount of a liquid formulation, by surface tension;
  - (ii) means to supply an appropriate measured volume of a liquid formulation to the spray nozzle;

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- (iii) means to eject a measured volume of liquid formulation from the spray nozzle as a jet;
  - (iv) means for exciting the jet of liquid formulation emitted from the spray nozzle to form a stream of droplets of liquid formulation;
  - (v) a charging electrode spaced co-axially in front of the spray nozzle, and so spaced that the stream of droplets, immediately they are formed, are within the charging field of the electrode; and
  - (vi) means for applying a voltage to the electrode.
6. Apparatus as claimed in claim 5 wherein the measured volume of the formulation is supplied to the nozzle by a metered valve or syringe pump.
7. Apparatus as claimed in claim 5 wherein the measured volume of the formulation is supplied by drawing into the nozzle the required amount from an external source by pipette action.
8. Apparatus as claimed in claim 5 where the measured volume of the formulation is contained in a demountable spray nozzle which is locatable on an appropriate receiving member in the apparatus.
9. Apparatus as claimed in claim 5 wherein the means for exciting the jet of liquid formulation emitted from the spray nozzle to form a stream of droplets is a piezoelectric or electromagnetic transducer.
10. Apparatus as claimed in claim 9 wherein the liquid jet formulation is excited at a frequency of 1-200kHz.
11. Apparatus as claimed in claim 5 wherein the charging electrode is in the form of a cylinder or annulus charged to a voltage of between 0.1 and 1000v.
12. Apparatus as claimed in claim 5 wherein at least the spray nozzle is suitable to be hand-held when in use.



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13. Apparatus as claimed in claim 5 comprising:

a body member 1 of a suitable size to be hand-held, having, mounted on one wall thereof, a guide 2 in the form of a short tube, the diameter of which approximates to the size of the eye to be treated, and, positioned in the portion of the wall of the body member 1 which lies within the guide tube 2, the outlet 3 of a narrow bore tube 4 which at its other end broadens to provide a wider bore section 5, positioned in a side wall of the body member 1, in which a spring-loaded piston 6 can operate;

a piezoelectric or electromagnetic transducer 7, located in the wall of the body member 1 and disposed in an annular manner around the outlet 3, and powered through electrical connections 8 and 9 from a voltage generator 10 via a frequency control unit 11, both of which are housed within the body member;

a demountable nozzle 12 which is capable of being detached from the apparatus, in order to be charged with the formulation to be administered, and then re-attached securely within the central orifice of the transducer 7 by a tight push fit to cooperate with the outlet 3;

and within the guide tube 2, a charging electrode 13 which is electrically insulated from the other parts of the apparatus, which is located co-axially with the transducer 7 and separated therefrom by a short distance, and which is charged to a suitable positive or negative potential through an electrical connection 14 from the voltage generator 10, its pulse frequency being controlled through the frequency control unit 11.

1 / 1

Fig.1.

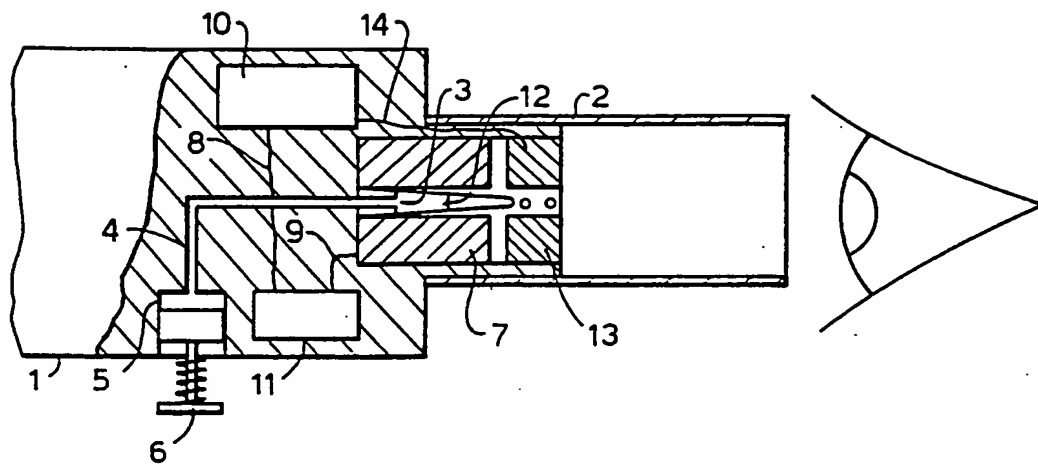
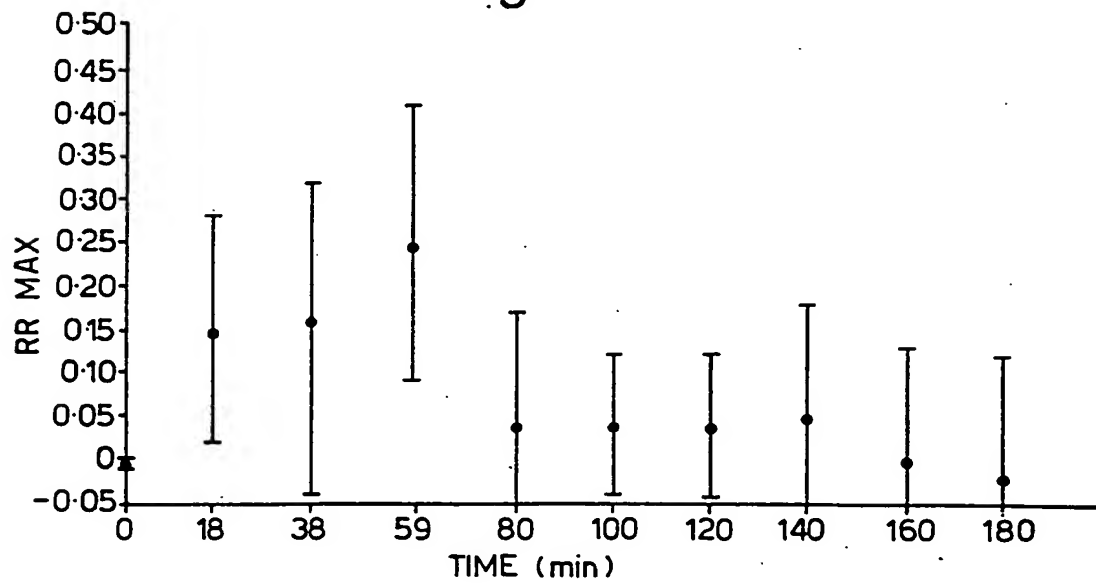


Fig.2.



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 95/00643

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 B05B17/06 B05B5/025

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 B05B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 011 269 (DR. KARL THOMAE GMBH) 28 May 1980 see page 3, line 20 - line 24 see page 4, line 4 - line 12 see page 7, line 21 - line 28 see page 10, line 19 - line 28; figures ---	1-11
X	REVIEW OF SCIENTIFIC INSTRUMENTS, no.6, June 1990, NEW YORK, US pages 1689 - 1693, XP166168 KYUN-JIN CHOI AND BRAIN DELCORIO 'GENERATION OF CONTROLLABLE MONODISPERSED SPRAYS USING IMPULSE JET AND CHARGING TECHNIQUES' see page 1689; figure 1 --- -/--	1-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/GB 95/00643

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